RANDOMIZED TRIALS OF SECONDARY PREVENTION PROGRAMS IN CORONARY HEART DISEASE: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: To determine whether secondary prevention programs for patients with established coronary artery disease (CAD) improve health outcomes.

Design: Randomized clinical trials (RCTs) of secondary prevention programs in patients with CAD were identified by searching Medline 1966-2004; the Cochrane Central Register of Controlled Trials, Issue 4, 2004; Embase 1980-2004; CINAHL 1982-2004; SIGLE 1980-2004; the Cochrane Effective Practice and Organization of Care Study Registry; bibliographies of published studies, and via contact with experts in the field and references provided by the Centres for Medicare and Medicaid Services. Studies were selected and data extracted independently by 2 investigators, and summary risk ratios were calculated using both the random and fixed effects models.

Results: A total of 41 RCTs (18 281 patients with CHD) were identified. Secondary prevention programs had positive impacts on processes of care: patients randomized to these programs were more likely to be prescribed efficacious medications and 20 out of 24 trials evaluating cholesterol profiles demonstrated improvements with

these programs compared to usual care (in 12 trials the improvements were statistically significant, with effect sizes in the small to moderate range). The summary RR was 0.89 (95% CI 0.79-1.01) for all-cause mortality, but this result differed over time with a RR of 0.97 (95% CI 0.82-1.14) for 12 month all-cause mortality in the 18 trials (9192 patients, p for heterogeneity=0.90, I-squared=0%) reporting this outcome and a RR of 0.53 (95% CI 0.31-0.92) for all-cause mortality at 24 months in the 4 trials (1367 patients, p for heterogeneity=0.44, I-squared=0%) reporting this outcome. The summary RR was 0.89 (95% CI 0.77-1.04) for recurrent myocardial infarction and 0.85 (95% CI 0.78-0.93) for hospitalization rates over a median follow-up of 12 months. There were no appreciable differences between group cardiac rehabilitation programs or secondary prevention programs focusing on individual education, counseling, and supervision in the primary outcomes we considered (mortality, hospitalizations, recurrent myocardial infarctions). Fourteen of the 26 trials evaluating quality of life or functional status reported statistically significantly better outcomes in those patients exposed to the intervention programs, although the effect sizes were generally small. Only 6 of these trials reported the costs of the

intervention- in 2 cases, the interventions were cost-saving**.** Another 2 trials reported significant reductions in health care resource use in patients exposed to secondary prevention programs compared to controls.

Conclusions: Secondary prevention programs improve processes of care, enhance quality of life/functional status, reduce hospitalizations, and reduce long-term mortality in patients with established CAD. Although these clinical benefits are likely to reduce health care costs, there is inadequate data to conclusively comment on the cost-effectiveness of these programs and specific components contained therein.

INTRODUCTION

Although cardiovascular death rates in North America have declined over the past two decades,[1] cardiovascular disease remains the most common cause of death (38% of all deaths in the United States in 2002), hospitalization, and physician office visits (over 80 million visits in 2002) and accounts for a large portion of total health care costs in the United States (estimated direct and indirect costs for 2005 are over $393 billion).[2] Using data from the National Health and Nutrition Examination Survey (NHANES 1999-2002), it is estimated that over 70 million Americans have one or more types of cardiovascular disease and over 13 million have known coronary artery disease (the proportion with undiagnosed disease is likely several fold higher).[2] Indeed, it is estimated that an American suffers a coronary event every 26 seconds, with 41% dying within a year.[2] Of course, coronary artery disease is not an American phenomenon and atherosclerotic cardiovascular disease is the leading cause of death worldwide.[3] A case-control study in nearly 30,000 subjects from 52 countries confirmed that 9 known coronary risk factors (Box 1) account for over 90% of the population

attributable risks for coronary disease in both men and women, in all age subgroups, and across all regions.[4]

Control of the CAD epidemic will require a multifaceted strategy targeting the 9 modifiable risk factors delineated in the INTERHEART study and including both primary prevention maneuvers (some designed for the general population and some targeting only high risk individuals) and secondary prevention programs (targeted at those with established disease).[5] Despite the abundant evidence base for CAD prevention,[6] health outcomes studies consistently demonstrate suboptimal control of cardiovascular risk factors due to gaps in the application of this evidence to clinical practice which contribute to sub-optimal patient outcomes.[7-15] Furthermore, even when some secondary prevention therapies are prescribed, patient compliance may be poor (from 43% to 75% at one year).[16,17]

Secondary prevention programs are increasingly advocated as a means to improve management and outcomes for patients with CHD. While numerous reviews have shown that cardiac rehabilitation programs improve outcomes in MI survivors,[18-22] these conclusions are based largely on trials which tested supervised exercise programs versus no exercise. As activity levels are

inversely proportional to cardiovascular mortality and exercise training confers substantial physiologic and clinical benefits,[23] it is not surprising that trials of exercise programs found positive treatment effects.

However, few of the trials included in these reviews evaluated comprehensive secondary prevention programs employing disease management approaches. Disease management has been defined as “a combination of patient education, provider use of practice guidelines, appropriate consultation, and supplies of drugs and ancillary services”.[24] To address this gap in the literature, we performed a systematic review of randomized trials of multidisciplinary disease management programs in patients with established CAD- in the 12 trials we identified (with 9803 patients), we found that multidisciplinary disease management programs improved processes of care (namely prescription of proven efficacious secondary prevention therapies) and risk factor profiles, reduced hospitalizations by 16% (95% confidence interval [CI] 6% to 24%), but did not have an appreciable impact on rates of death (RR 0.91, 95% CI 0.79-1.04) or recurrent myocardial infarction (RR 0.94, 95% CI 0.80-1.10).[25]

As current guidelines recommend that secondary prevention programs should not be restricted to supervised exercise programs but rather address the full range of modifiable risk factors,[26,27] we conducted the current systematic review to update our earlier work and to determine whether comprehensive secondary prevention programs (in contradistinction to exercise-only or similar single modality programs) prevent coronary events and/or death in patients with CAD.

METHODS

Searching for relevant studies:

We searched the following electronic databases to identify human randomized trials published in English: Medline 1966-2004; Cochrane Central Register of Controlled Trials, Issue 4, 2004; Embase 1980-2004; CINAHL 1982-2004; SIGLE 1980-2004. In order to identify recent publications, we also searched PubMed from January 2004 to December 2004 and conducted a cited reference search for our previous systematic review[25] in Web of Science (1999 to 2004). The searches (see Appendix A for listing of search strategy strings and results) were based on the following terms: case management, comprehensive health care, disease management, health services research, home care services, clinical protocols, patient care planning, quality of health care, rehabilitation, nurse led clinics, special clinics, and myocardial ischemia. To identify any studies missed by the literature searches, we hand-searched reference lists of all identified studies, as well as the reference list of a recent related review.[22] Finally, we screened references provided by the Centres for Medicare and Medicaid Services and content experts.

Selection of studies and abstraction of data:

Two of the investigators (AC and FM) independently reviewed the titles and abstracts of all citations to identify any studies reporting the impact of secondary prevention programs on death, MI, or hospitalization rates in patients with CAD (clinically manifest as angina, MI, or coronary revascularization). The full texts of all potentially relevant articles were obtained and reviewed by both investigators using pre-standardized data abstraction forms and *a priori* defined eligibility criteria. Any discrepancies were resolved by consensus.

All outcome data were extracted by AC and FM independently, and double-checked by BV. Outcomes were assigned according to the intention-to-treat principle and we accepted the definitions for each outcome used by the investigators in the primary studies. Original investigators were contacted to clarify the published data for any trials published in the past decade for which our outcomes of interest were not reported: authors for 9 of the 21 studies contacted provided further data.

Studies were excluded if they: were not randomized, were primary prevention studies (ie. restricted to patients without

documented CAD), evaluated single-modality interventions (such as exercise-only programs, yoga interventions, or telephone follow-up), tested interventions delivered to hospitalized patients rather than outpatients, did not include a “usual care” arm, tested interventions that were not provided by health professionals (such as letter reminders, self help groups, self-directed interventions, or general health promotion interventions), or reported outcome data from less than 50 subjects. Studies in which patients with multiple diseases were enrolled were included if the outcomes for patients with coronary heart disease were reported separately or that data was provided by the study principal investigator when contacted.

Two of the investigators (AC and FM) independently assigned each reported intervention to one of 3 *a priori* defined groups: (1) Comprehensive Cardiac Rehabilitation (which included exercise as well as group education and counseling sessions about coronary risk factor management), (2) Cardiac Rehabilitation without exercise component (programs which included group education and counseling sessions about coronary risk factor management, but no structured exercise component), or (3) Individual Counselling (programs, usually delivered by specially trained nurses, involving

individual education and counseling sessions and individual follow-up, either in person or by telephone, to encourage coronary risk factor optimization). It should be noted that patient education was a key component of all 3 types of interventions (see Table 1 for a fuller description of the program in each included trial).

Statistical analysis:

Analyses were performed using RevMan 4.2 (The Cochrane Collaboration 2004). Our primary outcome was all-cause mortality at 12 months. Secondary outcomes that were meta-analyzed were recurrent myocardial infarctions and hospitalizations (although we attempted to obtain data on all-cause hospitalizations wherever possible, for some trials we were only able to obtain cardiovascular hospitalizations even after contact with the primary study authors). We defined "hospitalization rate" as the number of patients in each trial arm who were hospitalized at least once (thus, each patient could only contribute one event to these analyses).

As the outcomes were relatively common, risk ratios were calculated and the I^2 statistic was used to assess for heterogeneity in each outcome of interest. Studies were combined using the DerSimonian and Laird random effects model and the Peto fixed

effects model- where there was significant inter-trial heterogeneity, the results of the random effects model are reported, where there was no evidence of heterogeneity, the fixed effects results are presented. Analyses were conducted for each of the three types of programs: comprehensive cardiac rehabilitation, group cardiac rehabilitation (without exercise component), and individual counseling. For the primary analysis, we used data from the 12 month follow-up or, when unavailable, from the follow-up period closest to 12 months. We also conducted analyses for all programs combined using the various follow-up periods reported (6, 12, 24, 36, 48, 56, 60, and 72 months).

We described, but did not meta-analyze, the following outcomes: effects on major cardiovascular risk factors (cholesterol, smoking, blood pressure), use of proven efficacious therapies, patient quality of life, and patient functional status or symptom scores. These were evaluated and categorized as: statistically significant benefit seen in the intervention arm versus the control arm; trend towards better outcomes in the intervention arm, but did not reach statistical significance; or, no appreciable difference between the intervention and control arms. In order to standardize the

reporting of results for non-dichotomous outcomes (such as change in cholesterol or blood pressure levels, quality of life, or functional status scores), we calculated standardized effect sizes by dividing the absolute difference between intervention and control arms by the standard deviation in the control arms. By convention, effect sizes <0.20 are considered trivially small, 0.50 moderate, and >0.80 large.

RESULTS

Study selection and evaluation:

Overall we identified 6,336 citations from electronic databases (n=6,207), reference lists (n=36), and the Centres for Medicare and Medicaid Services (n=93). We reviewed 231 full manuscripts for potential inclusion. We excluded 180 of these studies after detailed evaluation; the reasons for exclusion are detailed in Figure 1 and Appendix A (a full list of excluded studies is included in Appendix B).

Disagreement among the reviewers regarding eligibility of the studies occurred on 16 occasions for a kappa value of 0.81. All disagreements were resolved by consensus.

Of the randomized trials eligible for inclusion,[28-79] 10 were reported in more than one publication. Two trials reported different endpoints in two separate publications.[28,29,57,58] One trial[30] reported the outcomes for all patients enrolled (only 56% of whom had cardiac disease) and, in a separate publication[31], provided details of event rates in the subgroup of patients with cardiac disease. The WHO Trial[32] included 24 collaborating centres; however, the original investigators excluded 7 sites because of poor subject follow-up and 4 sites due to significant differences at baseline

between the intervention and control arms. We included the 3-year outcome data from the remaining 13 sites as one trial for the purposes of this analysis, an approach validated by the non-significant tests for statistical heterogeneity for all-cause mortality (Q=15.7, 11 df, p=0.16) and MI (Q=15.9, 11 df, p=0.15) and the fact that the summary risk ratios for both endpoints were identical under the random and fixed effects models. While the two Finnish centres in the WHO Trial published their results separately (and for multiple follow-up periods), we included only their 3-year outcome data with the other 11 WHO sites for consistency of data presentation.[33-35] In five cases, we identified studies that reported longer follow-up data from another relevant trial.[36-40]

Studies included in the systematic review:

Summary data from the 41 unique randomized trials eligible for this systematic review are presented in Table 1.[28-79] In all of the trials, patients randomized to the control groups received usual care (this was generally undefined). One trial[41] is presented twice in the Table 1 because it had two intervention groups (comprehensive cardiac rehabilitation and group counseling) as well as a usual care control arm.

Our search retrieved 29 trials not included in our previous systematic review (which was limited to the pre-1999 literature)[25] and 22 trials not included in a more recent systematic review of cardiac rehabilitation (which was limited to the pre-2003 literature)[22].

Quantitative data synthesis:

All-cause mortality: Only one of the 27 trials reported a statistically significant survival benefit with the intervention (Table 2, Figures 2-4). The summary RR for all 27 trials reporting this outcome (13 625 patients, random effects RR 0.89 [95% CI 0.79-1.01]; fixed effects RR 0.89 [95% CI 0.79-1.01]) confirms that these interventions have not yet been shown to improve survival at 12 months. There was no significant statistical heterogeneity between trials (p=0.82, I-squared=0%) and the 12 month all-cause mortality rate in the control patients was 7%.

Although there was no appreciable difference in the treatment effects with any of the 3 types of secondary prevention programs (Table 2, Figures 2-4), there were differences in effect over time-while the RR for all-cause mortality was 0.97 (95% CI 0.82-1.14) in the 18 trials (9192 patients, p for heterogeneity=0.90, I-squared=0%)

reporting 12 month outcome data, the RR for all-cause mortality was 0.53 (95% CI 0.31-0.92) in the 4 trials (1367 patients, p for heterogeneity=0.44, I-squared=0%)[40,41,43,77] reporting 24 month outcome data. The 24 month all-cause mortality rate in the control patients was 5.5% and the number needed to treat to prevent one death in the next 24 months was 39. Furthermore, pooling the data from the 4 trials (2225 patients)[28,40,42,39] reporting follow-up data from at least 5 years after initiation of the intervention program demonstrates these programs had a sustained beneficial effect: the RR for all-cause mortality was 0.76 (95% CI 0.62-0.92) at 5 years with no appreciable heterogeneity between the trials (p=0.94, I-squared=0%).

Re-infarction Rate: One of the 16 trials reporting this endpoint (Table 2, Figures 5-7) detected a significant difference between intervention and control patients and the summary RR for 12 month re-infarction rate for all 9210 patients was 0.89 (95% CI 0.77-1.04). There was no significant statistical heterogeneity between trials (p=0.31, I-squared=13%) and the 12 month re-infarction rate in the control patients was 7%. There was no appreciable difference in the treatment effects with any of the 3 types of secondary prevention

programs (Table 2, Figures 5-7), nor were there any differences in effect over time.

Hospitalization Rate: Two of the 13 trials (5751 patients) reporting hospitalization rates detected a significant difference between intervention and control patients and the summary random effects RR for hospitalization rates for all 5751 patients was 0.85 (95% CI 0.78-0.93)- see Figure 8. Although there was no significant statistical heterogeneity between trials (p=0.24, I-squared=20%), we report this result using the random effects model as some trials reported data on all-cause hospitalizations and some only cardiovascular hospitalizations. The hospitalization rate in the control patients was 33% and the number needed to treat to prevent one hospitalization was 21 (median length of follow-up in these trials was approximately 12 months).

Restricting our analysis to the 9 trials (3653 patients) which reported all-cause hospitalization rates reveals a summary random effects RR of 0.84 (95% CI 0.74-0.97). Restricting our analysis to the 7 trials (3233 patients) which reported cardiovascular hospitalization rates reveals a summary random effects RR of 0.76 (95% CI 0.58-0.98).

Sensitivity Analyses: Analyses failed to reveal any effect of publication year on the observed results (data not shown).

Publication Bias: There was no evidence of publication bias (see Funnel Plot in Figure 9). The results of Begg's Test (p=0.62) and Egger's Test (p=0.61) confirm this.

Processes of Care: Twenty-four trials tested the impact of these disease management programs on cardiovascular risk factors, with 20 demonstrating better cholesterol profiles in patients randomized to the interventions, although the differences were statistically significant in only 12 trials and the effect sizes were generally small to moderate (Table 3). Of the 20 trials that assessed the use of proven efficacious medications, 8 demonstrated statistically significantly better application of at least one of these therapies in the intervention patients, 2 demonstrated better prescribing in intervention patients but did not achieve statistical significance, and 10 failed to demonstrate any appreciable difference between intervention and control patients (Table 3). It should be noted that in many cases the failure to demonstrate improved processes of care with the intervention was because of improved risk factor management in control patients- for example, in one study that

followed patients for over 4 years, 55% of controls had been exposed to comprehensive secondary prevention clinics by the close of the study.[37]

Other Endpoints: Fourteen of the 26 trials evaluating quality of life or functional status reported statistically significantly better scores in those patients exposed to the intervention programs, although the effect sizes were generally small (Table 3). Only 6 of these trials[30,44,49,50,65,66] described the costs of the intervention- while 2[30,50] reported that their intervention was cost-saving, none performed formal cost-effectiveness analyses. Another trial did not report costs, but did report that patients in the intervention arm had less visits to physicians as outpatients, less emergency room visits, less laboratory testing, and less total hospital days in follow-up than control patients.[78] Another trial reported statistically significantly lower inpatient bed days in intervention arm patients over 4 years of follow-up compared to controls (Dr. M. Vale, personal communication, January 10 2005).[76]

DISCUSSION

In summary, the weight of the published randomized trial evidence suggests that comprehensive secondary prevention programs positively impact on processes of care (risk factor profiles, use of proven efficacious therapies) which are closely linked to subsequent morbidity and mortality in patients with CAD.[80] Pooling the data from those trials which reported subsequent rates of MI does reveal a trend towards an 11% reduction in recurrent MIs over a median follow-up of 12 months which is not statistically significant; the majority of these programs also demonstrate improved symptom scores, exercise tolerance, or quality of life in participants. The mortality benefit derived from participation in the secondary prevention programs we identified (47% at 2 years [number needed to treat to prevent one death in 24 months=39] and 24% at 5 years) became apparent with longer lengths of follow-up, a fact which is not surprising considering the natural history of atherosclerotic CAD (ie. changes in coronary risk factors would not be expected to produce immediate improvements in atherosclerotic plaque stability or coronary artery diameter). There was a statistically significant 15% reduction in hospitalizations (driven by a statistically significant 24%

reduction in cardiovascular hospitalizations) over a median follow-up of 12 months (number needed to treat to prevent one hospitalization=21). These early beneficial effects on hospitalizations mirror the findings of a recent systematic review of multidisciplinary strategies for patients with heart failure which found that such interventions reduce hospitalizations by 25% within 6 months of implementation.[81]

Although some comprehensive lifestyle modification programs under consideration by the Medicare Coverage Advisory Committee, including the Ornish Program, were not included in our analysis (because the relevant randomized trial evidence reported data on less than 50 patients), our analyses extend the evidence base from these other programs to prove significant benefits on hard clinical endpoints. The Lifestyle Heart Trial evaluated the Ornish Program in 48 patients with CAD and demonstrated that a 12 month program emphasizing a low fat vegetarian diet, smoking cessation, stress management, and moderate exercise with group psychosocial support and counseling sessions improved coronary risk factors and significantly decreased the frequency and severity of angina in intervention patients vs. controls.[82] Furthermore, quantitative

coronary angiography demonstrated regression of coronary atherosclerosis in 82% of intervention patients versus 42% of control patients (p=0.009).[82] It is worth noting that the control patients in the Lifestyle Heart Trial were following a Step II diet of the National Cholesterol Education Project. Subsequent studies have confirmed that this multi-component cardiac rehabilitation program can be successfully taught and implemented at various American sites[83] and would likely be cost-saving.[84] However, it should be noted that while this economic analysis suggested that care cost reductions in the order of 30% to 60% within the first year were possible, the analyses are based on observational data (two concurrent cohorts followed for one year in one study, matched claims data analyses in another study, and two studies comparing actual costs after participation in the Ornish Program versus predicted costs) rather than randomized trial evidence.[84] Of course, a one year time horizon is likely too short for fully evaluating the cost-effectiveness of secondary prevention programs and studies with 5 and 10 year time horizons are needed (and ongoing).

Previously published systematic reviews of cardiac rehabilitation in survivors of myocardial infarction have reported

survival benefits in the order of 20-24%. However, most of the trials included in those overviews evaluated single modality exercise-based interventions (and thus were not included in our overview). For example, a recently published meta-analysis reported a statistically significant 20% reduction in all-cause mortality in 8432 patients; however, closer inspection of their report reveals that 40% of the data in their mortality analysis came from 13 trials which evaluated exercise-only programs and 2 trials which were excluded from our systematic review because of lack of a usual care control arm.[22] As activity levels are inversely proportional to cardiovascular mortality and exercise training confers substantial physiologic and clinical benefits (including changes in endothelial function, autonomic tone, inflammatory markers),[23,85] it is not surprising that those trials found greater treatment effects than the trials included in our review (which evaluated multidisciplinary secondary prevention interventions that were not primarily exercise-based). However, the choice of programs to evaluate in our review was driven by current guideline recommendations that secondary prevention programs should not be restricted to supervised exercise programs alone.[26,27] Our systematic review is the first to prove that secondary prevention

programs which are delivered by health care providers and are not restricted to supervised exercise training do provide tangible reductions in clinically relevant endpoints such as hospitalization and death in addition to their well documented beneficial effects on patient risk factor profiles and quality of life/functional status.

Why didn't the trials reporting 12 month outcome data (including over 9000 subjects) demonstrate a statistically significant survival benefit? First, 12 months was clearly too short to show a clear impact on mortality- a fact supported by the known pathophysiology of atherosclerotic CAD and by the data demonstrating a significant survival benefit in those studies reporting outcomes over 2 years or more. It should be emphasized that studies which did evaluate coronary angiographic lesions at baseline and after 12 months did report statistically significant regression rates in patients compliant with comprehensive lifestyle modifications within 12 months even without significant changes in metabolic profiles or medication usage.[39,82] Second, the patients included in these studies were at sufficiently low risk over the first year after enrollment that the likelihood of detecting a beneficial effect was remote- indeed, the control event rates in these trials were substantially lower than

those in other trials enrolling patients with clinically overt CAD. Third, the incremental benefit of secondary prevention programs over usual care may be very small in the settings in which the trials were carried out (where management in the “usual care” arm may be close to optimal already). Indeed, secondary prevention programs are likely to be most beneficial in those settings where usual care is sub-optimal. Finally, it is possible that the labelling of patients with one disease for special attention in a disease-specific management program may have led to sub-optimal care for their co-morbid conditions and, as a result, no real difference in all-cause mortality.[86]

The overall effectiveness of secondary prevention programs should be interpreted in the context of the unexplained inconsistencies in effectiveness between different types of programs. As the programs were evaluated as single entities, it was not possible to ‘open the black box’ to identify what the key characteristics of successful programs were, which components were most influential, or how particular program or setting characteristics influenced outcomes. The particular mechanisms of effect of interventions remain poorly understood. Translation of the theoretical benefits of

secondary prevention programs into real-world patient benefit is also dependent on suitable patients being referred to, accessing, and completing the programs. Health outcomes research has consistently demonstrated that, even in publicly funded health care systems where access is free, only a minority of patients (less than one quarter to one half) ultimately access these programs.[10,87,88] Moreover, those groups that are less likely to be referred, attend, and complete programs are often those in greatest need of additional support and risk reduction, such as women, the elderly, low income groups, and ethnic minorities.[87] These groups were underrepresented in the studies reviewed.

Generalizability of the trial data:

As can be seen from Table 1, these trials enrolled relatively young patients- some even excluded patients over the age of 65. This raises potential concerns about the generalizability of our findings to this increasingly large population that is especially vulnerable to CAD. However, there is evidence that elderly patients demonstrate similar benefits after secondary prevention programs as younger people.[89-91] For instance, exercise training of elderly patients can provide a significant improvement in exercise tolerance similar to that

experienced in younger individuals.[92] While it is now less common for programs to have age-based restrictions for entry, older people are frequently excluded from programs due to a lack of program capacity to address their complex health needs or limited resources.[93,94] The effectiveness of programs for older patients may therefore be dependent not only on program content but also on program capacity to provide effective care to older patients who frequently have multiple co-morbidities.

Women were also underrepresented in the studies reviewed and data was not available to examine results by gender. This imbalance is significant because cardiac disease remains the leading cause of death for women in most of the developed world,[95] but is often viewed erroneously as principally being a “disease of men”. Sex differences in the investigation and management of CAD have been evident for many years.[96] Consequently, the need for improved and more responsive management of CAD in women has now been recognized by international guidelines.[96] While there is no evidence of any gender-based barriers to program benefit, women are consistently identified as being less likely to access programs.[97] To increase the strength of evidence supporting the

benefits of programs to women, more women should be included in study samples and data presented that examines the effectiveness of programs in males versus females.

Finally, as with any intervention proven efficacious in trial settings, the applicability of this evidence to the “real-world setting”, where compliance is likely to be highly variable and generally lower than that observed in trial participants, is a potential concern. While this may lead some to conclude that the results we report should be viewed as a “best case scenario” for the impact of secondary prevention programs, we disagree as we believe this view neglects that fact that randomized trial participants assigned to the control arm also receive care which is better than usual care. Indeed, as we pointed out earlier, the incremental benefit of secondary prevention programs over usual care may be very small in the settings in which these trials were carried out, where management in the “usual care” arm was often close to optimal already. Indeed, it seems likely that secondary prevention programs will be more beneficial in other settings (perhaps more akin to the “real world” of current clinical practice) where usual care is sub-optimal.

Limitations of this Review:

As with all systematic reviews, this study has a number of potential limitations. The most obvious (the lack of blinding in outcome ascertainment, lack of detail on whether randomization was conducted properly or whether allocation concealment was achieved, and our inability to identify unpublished studies- although we did not find any evidence for publication bias) arise from the primary data and, as all tend to result in over-estimation of any treatment effects,[98] these factors should be taken into account when interpreting our summary estimates. Our interpretation of these trials and the generalizability of the programs described is hampered by the imprecise descriptions of the interventions and the lack of data to determine the incremental benefits of the various components of each intervention. While some may criticize our choice of primary endpoints as being too broad to detect differences in “cardiac” morbidity and mortality, we believe that it is most appropriate to look at all-cause mortality or hospitalization as interventions to reduce resource use in one area can have unanticipated effects in another. Finally, we are unable to make a definitive comment on the cost-

effectiveness and economic impact of the programs tested in these trials due to the paucity of data.

In summary, although there was substantial variability in the interventions offered and the studies enrolled highly selected populations, secondary prevention programs do improve processes of care, coronary risk factor profiles, and functional status/quality of life. While the optimal mix of interventions, including their frequency and duration, are unclear, these programs do reduce hospitalizations and long-term mortality in patients with known CAD. While these programs appear to reduce health care resource use, their cost-effectiveness has been inadequately evaluated thus far in the literature. Thus, we believe that any policy decisions to implement secondary prevention programs on a wide scale should be accompanied by plans to rigorously evaluate long-term clinical and economic outcomes in participants and non-participants.

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Don't have full report (but potentially relevant to the review, may be included in final report if we get data from the author before the mid-February final deadline):

Bell JA. Comparison of a multi-disciplinary home based cardiac rehabilitation programme with comprehensive conventional rehabilitation in post-myocardial infarction patients (PhD thesis). London, United Kingdon: University of London; 1998.

Box 1: Modifiable coronary risk factors (adapted from reference 4)

Modifiable Risk Factor	Prevalence in cases with myocardial infarction	Population Attributable Risk (99% CI)	Odds Ratio (99% CI) adjusted for age, gender, and smoking
Smoking	65%	36% (34% to 39%)	2.3 (2.1-2.4)
Dyslipidemia	33%	54% (50% to 59%)	3.9 (3.4-4.4)
Diabetes Mellitus	18%	12% (11% to 14%)	3.1 (2.8-3.4)
Hypertension	39%	23% (22% to 25%)	2.5 (2.3-2.7)
Abdominal Obesity	46%	34% (30% to 37%)	2.2 (2.1-2.5)
Psychosocial Factors	-	29% (23% to 36%)	2.5 (2.2-2.9)
Daily consumption of fruits and vegetables	36%	13% (10% to 17%)	0.7 (0.6-0.8)
Regular physical activity	14%	26% (20% to 32%)	0.7 (0.7-0.8)
Regular alcohol consumption	24%	14% (9% to 20%)	0.8 (0.7-0.9)
All of the above combined	-	90% (88% to 92%)	129.2 (90.2-185.0)

In the INTERHEART Study, “dyslipidemia” was defined as ApoB/ApoA1 Ratio in top quintile vs. lowest quintile; “abdominal obesity” was defined as waist/hip ratio > 0.90 in men and >0.83 in women; “psychosocial factors” was defined as positive exposure to depression, perceived stress at work or home, moderate or severe financial stress, low locus of control, and/or major life events; “regular physical activity” was defined as moderate or strenuous exercise for at least 4 hours per week; “regular alcohol consumption” was defined as 3 or more times per week.

Table 1: Description of studies included

Study	Sample Size	Study Population (Location)	Mean Age	% Male	Key Components of Intervention	Duration of Intervention
Comprehensive Cardiac Rehabilitation (15 trials, 3896 patients)						
Sivarajan (1982)	258 (170 in control and comprehensive secondary prevention arms)	Patients younger than 70 years discharged after AMI (USA)	57	>80%	Exercise program plus group education/counseling sessions about risk factor management	3 m
Vermeulen et al. (1983)	98	Males 40-55 yrs, discharged after AMI (Netherlands)	49	100%	Multidisciplinary team (details not given) involved in exercise rehabilitation, social and psychological supports for patients	1.5-2 m
Bengtsson (1983)	87	Patients aged <65 years, one year after AMI (Sweden)	56	85%	Rehabilitation program involving physical assessment and training by physiotherapy and counseling.	3m
World Health Organization* (1983)	1,735	Males < 65 yrs, discharged after AMI (Europe)	53	100%	Multidisciplinary team (components differed at each center) involved in patient health education and supervised exercise program	36 m
Oldridge (1991)	201	Patients discharged with diagnosis of AMI and evidence of anxiety or depression (Canada)	52	89%	Exercise prescription, supervised training and behavioral counseling	2 m
PRECOR (1991)	182	Males <65 years, discharged after AMI (France)	51	100%	Two intervention arms, one of which was: Comprehensive cardiac rehabilitation (supervised exercise program, relaxation training, risk factor management, education)	1.5 m
Fridlund et al. (1991)	178	Patients <65 years discharged after AMI (Sweden)	56	87%	Nurse-led rehabilitation program addressing lifestyle, stress and social support.	6
Engblom (1992)	228	Patients younger than 65 years, discharged after CABG (Finland)	54	88%	Group education, individual counseling (with physician and dietician) about diet and physical activity, supervised exercise training	0.75 m
Heidelberg Trial (Schuler 1992 and Niebauer 1997)	113	Males with CAD on angiography (Germany)	54	100%	Education about diet and exercise, exercise program with individual and group training sessions	12 m

Johnston et al. (1999)	100	Patients ≤ 70 years hospitalized for 1st time myocardial infarction (UK)	56	65%	Nurse-led inpatient and outpatient cardiac rehabilitation program containing education, support for risk factor change and psychological effects.	1.5 m
Lisspers et al (1999)	93	Patients <65 after PCI (Sweden)	53	37	Comprehensive residential (health education, behavioural change) containing skills training, habit rehearsal on stress management, smoking, diet, exercise and smoking; followed by outpatient program of self observation and reporting of risk factors with follow up support.	12m
Sundin et al. (2003)	132	Male patients <70 years after PCI, AMI or CABG (Sweden)	59	100%	Group-based multidisciplinary program addressing stress management, diet and exercise using lectures and skills training	12m
Yu et al. (2003)	112	Obese patients attending cardiac rehabilitation after acute MI or after percutaneous coronary intervention (China)	62	79%	Exercise program with group education classes about risk factor modification	2.5 m
Vestfold Heartcare Study (2003)	197	Patients discharged after acute coronary syndrome, CABG, PCI (85%); plus patients followed in clinic with stable CAD (15%) (Norway)	55	82%	Supervised exercise program, dietary advice, risk factor management education and individual plus group counseling involving a multidisciplinary team (physician, nurse, dietician, physiotherapist)	24 m
Marchionni et al (2003)	270	Patients older than 45 years discharged after AMI (Italy)	69	71%	Supervised exercise training and education/counseling about risk factor management, optional monthly support groups	2 m
Group Cardiac Rehabilitation without exercise component (4 trials, 2671 patients)						
Stern (1983)	106 (64 in control and group counseling arms)	Patients aged 30-69 years with recent MI (USA)	54	83%	Nurse and psychiatrist/social worker led group education and counseling sessions (12 sessions)	3 m
PRECOR (1991)	182	Males <65 years, discharged after AMI (France)	51	100%	Two intervention arms, one of which was: Group Counselling Program (group education and counseling led by physician, psychiatrist, and nutritionist)	1.5 m

Jones et al. (1996)	2328	Patients discharged home within 28 days of AMI (United Kingdom)	62	73%	Nurse and psychologist regularly saw participants for education, counselling, and relaxation/stress management training	1.75 m
DIET (2001)	97	Patients with known CAD and hyperlipidemia in specialty clinics (USA)	65	70%	Nurse-led education (group) and provision of written materials about diet and physical activity	12 m
Individual Counselling (23 trials, 11 896 patients)						
SCRIP (1994)	300	Patients < 75 yrs referred for angiography for known or suspected CAD (USA)	56	86%	Nurse-managed patient education and algorithm-driven management of risk factors, exercise program, frequent telephone and clinic visits with nurse	48 m
DeBusk et al. (1994) and Taylor (1997)	585	Patients $\leq$ 70 yrs discharged after AMI (USA)	57	79%	Nurse-managed patient education and counselling, exercise program, frequent telephone contact, and algorithm-based lipid therapy	12 m
Fitzgerald et al. (1994)	668	Patients > 45 yrs discharged from a general medicine in-patient service (2/3 with heart disease) and being followed at the general medicine clinc of a Veterans Affairs hospital (USA)	65	100%	Nurse-managed patient education, coordination of care, frequent telephone contact, and protocol-driven systematic assessments for unmet socio-medical needs	12 m
Naylor et al. (1994)	276 (142 with cardiac disease)	Patients > 70 yrs discharged from a tertiary care hospital with either CAD or heart failure (USA)	76	49%	Comprehensive discharge planning protocol with gerontologic nurse providing education, coordinating care, and maintaining telephone contact for 2 weeks	0.5 m
Cupples et al. (1994 and 99)	688	Patients <75 years with angina for at least 6 months identified from general practice records (UK)	63	59%	Individual nurse-led personalized health promotion program every 4 months	24 m
M-HART (1997)	1376	Patients discharged after AMI (Canada)	59	66%	Nurse contacted patients monthly by telephone, providing education and advice and screening patients for psychological distress- nurses referred patients to other health care resources as needed	12 m
Carlsson et al (1997)	168	Patients aged 50-70 years discharged after AMI (Sweden)	62	75%	Nurse-run education program (individual and group), exercise training program, nurse clinic visits	12 m
Carlsson et al	530	Patients aged 50-70 years discharged	62	79%	Individualized assessment and nurse	12 m

(1998)		after AMI, CABG or PCI (Sweden)			counseling on risk factors and diet	
Campbell et al. (1998), with longer term f/u reported in Murchie et al (2003)	1343	Patients <80 yrs old with documented CAD recruited from general practice records (United Kingdom)	66	58%	Regular followup at secondary prevention clinics run by nurses, promoting medical and lifestyle approaches to prevention	12 m
Jolly et al. (1999)	597	Patients with AMI or recent onset angina discharged from hospital or seen in a chest pain clinic (United Kingdom)	64	71%	Cardiac liason nurse coordinated care between discharging service and family physician, patients given personal health record and prompts for follow-up	12 m
Naylor et al. (1999)	363 (202 with cardiac disease)	Patients $\geq$ 65 years discharged from a tertiary care hospital with either CAD or heart failure or after CABG/heart surgery (USA)	75	50%	Nurse-led patient education, coordination of home care, at least 2 home visits, use of a standardized protocol to optimize medications, and weekly telephone contact for 1 month	1 m
Allison et al. (1999)	152	Patients not treated with lipid lowering medication that completed cardiac rehabilitation after an acute coronary event (USA)	64	82%	Nurse-led follow up program every 6 weeks after start or change in lipid lowering therapy, including diet and exercise advice and lipid lowering medications.	6 m
Allison et al. (2000)	326	Patients attending emergency room with confirmed unstable angina (USA)	58	56%	Nurse-intervention including lipid management, referral to support services, counseling on risk factors and physician collaboration on abnormal results, 2 1-hour sessions at least 6 and 25 days after discharge	1 m
Moher et al. (2001)	1906	Patients 55-75 years identified in family practices with established CAD (UK)	66	68%	Nurse-led clinic providing support for risk factor change using electronic disease register and recall system	1 m
Stagmo et al. (2001)	241	Patients 50-69 years hospitalized in a CCU due to MI or previous CABG (Sweden)	62	78%	Hospital-based secondary prevention program	12 m
McHugh et al. (2001)	98	Patients on a waiting-list for elective CABG (UK)	62	76%	Shared nurse-led care program of monthly health education and motivational interviewing	7 m
Higgins et al	105	Patients discharged after PCI	48	90%	Nurse-led individualized education, risk	12 m

(2001)		(Australia)			factor goal setting and self-monitoring with telephone feedback, 3 home visits	
Allen et al. (2002)	228	Patients ≤ 75 years discharged after CABG or PCI who had hypercholesterolemia (USA)	60	63%	Nurse practitioner case management in partnership with patients' primary provider (nurse-directed education and lifestyle modification advice, nurse clinic visits, nurse prescribed medications if necessary, f/u telephone calls)	12 m
COACH pilot (2002)	245	Patients ≤ 75 years discharged after coronary revascularization procedure (Australia)	61	75%	Personal coaching by dietician via 5 telephone sessions and 5 mailings to achieve coronary risk factor targets (education, negotiated lifestyle plan, emphasis on followup with primary care provider and empowerment to ask for medication, repeated measurements)	6 m
COACH (2003)	792	Patients discharged from 6 hospitals after CABG, PCI, AMI, coronary angiography (Australia)	59	77%	Personal coaching (delivered by nurses or dieticians) via 5 telephone sessions and 5 mailings to achieve coronary risk factor targets (education, negotiated lifestyle plan, emphasis on followup with primary care provider and empowerment to ask for medication, repeated measurements)	6 m
ELMI Trial (2003)	302	Patients discharged from 2 tertiary-care cardiac rehabilitation programs (Canada)	64	83%	Personal coaching by case manager delivered via telephone and in-person counseling sessions; if suboptimal coronary risk factors at 6 months, treatment algorithms with cover letter from cardiologist mailed to primary care physicians	12 m
Young et al (2003)	146	Patients discharged home after AMI (Canada)	69	60%	Patient education, at least 6 home visits by nurse, nurse communication with primary care providers, and nurse-initiated referral for specialty care (based on standardized pathway)	2 m
REACH Trial (2004)	756	Patients aged 30-80 years discharged from tertiary care hospital with documented coronary disease (USA)	64	71%	Nurse-based education and counseling about cholesterol and target levels delivered via telephone (4 calls in 9 m) and mailed	12 m

					educational materials about a variety of secondary prevention manoeuvers	

* As outlined in text, the results for 13 of the 24 collaborating centers in the World Health Organization Trial are included here. Reasons for the exclusion of the other 11 centers are given in the text.
CHD=coronary heart disease; CHF=congestive heart failure; SCRIP= Standard Coronary Risk Intervention Project; COACH= Coaching patients On Achieving Cardiovascular Health Study; ELMI= Extensive Lifestyle Management Intervention ; REACH= Reinforcing Education About Cholesterol; CABG= Coronary Artery Bypass Grafting surgery ; PCI= Percutaneous coronary intervention; CCU= Coronary Care Unit; AMI= Acute Myocardial Infarction

Table 2: Impact of interventions on all-cause mortality and recurrent myocardial infarctions.

Study	Length of Follow-up	All-cause mortality (#events/total # patients)			Recurrent Myocardial Infarctions* (#events/total # patients)		
		Intervention Arm	Control Arm	Risk Ratio	Intervention Arm	Control Arm	Risk Ratio
Comprehensive Cardiac Rehabilitation							
Sivarajan	6 m	3/86	2/84	1.47 (0.25, 8.55)	NR	NR	NR
Vermeulen et al.	60 m	2/47	5/51	0.43 (0.09, 2.13)	4/47	9/51	0.48 (0.16, 1.46)
Bengtsson et al.	12 m	10/81	6/90	1.85 (0.70, 4.87)	2/81	4/90	0.56 (0.10, 2.95)
WHO	36 m	146/893	161/842	0.86 (0.70, 1.05)	150/893	139/842	1.02 (0.82, 1.26)
Oldridge et al.	12 m	3/99	4/102	0.77 (0.18, 3.36)	NR	NR	NR
PRECOR** - comprehensive rehabilitation arm	24 m	0/60	4/61	0.11 (0.01, 2.05)	4/60	6/61	0.68 (0.20, 2.28)
Fridlund et al.	12 m	9/87	14/91	0.67 (0.31, 1.47)	4/87	14/91	0.30 (0.10, 0.87)
Engblom et al.	12 m	12/119	13/109	0.85 (0.40, 1.77)	8/119	16/109	0.46 (0.20, 1.03)
Heidelberg Trial	12 m 72 m	2/56 5/43	1/57 8/53	2.04 (0.19, 21.82) 0.77 (0.27, 2.18)	2/56 3/43	4/57 4/53	0.51 (0.10, 2.67) 0.92 (0.22, 3.91)
Lisspers et al	12 m	0/46	1/41	0.30 (0.01, 7.12)	NR	NR	NR
Vestfold Heartcare Study	24 m	2/98	1/99	2.02 (0.19, 21.92)	4/99	3/99	1.33 (0.72, 1.05)
Marchionni et al	12 m	7/180	3/90	1.17 (0.31, 4.41)	1/180	3/90	0.17 (0.02, 1.58)
Sub-Total:	***12 trials***	***196/1852***	***215/1717***	***0.87 (0.73, 1.05)***	***177/1622***	***198/1490***	***0.86 (0.71, 1.04)***
Group Cardiac Rehabilitation without exercise component							
Stern	12 m	0/35	1/29	0.28 (0.01, 6.57)	3/35	2/29	1.24 (0.22, 6.94)
PRECOR** -counselling arm	24 m	5/61	4/61	1.25 (0.35, 4.43)	4/61	6/61	0.67 (0.20, 2.25)
Jones et al.	6 m 12 m	53/1168 79/1168	58/1160 84/1160	0.91 (0.63, 1.31) 0.93 (0.69, 1.26)	 43/1168	 48/1160	 0.89 (0.59, 1.33)
Sub-Total:	***3 trials***	***84/1264***	***89/1250***	***0.94 (0.70, 1.25)***	***50/1264***	***56/1250***	***0.88 (0.61, 1.28)***
Individual Counselling							
SCRIP	12 m 24 m 36 m 48 m	1/145 1/145 2/145 3/145	0/155 2/155 2/155 3/155	3.21 (0.13, 78.06) 0.53 (0.05, 5.83) 1.07 (0.15, 7.49) 1.07 (0.22, 5.21)	5/145 5/145 5/145 6/145	0/155 3/155 6/155 11/155	11.75 (0.66, 210.69) 1.78 (0.43, 7.32) 0.89 (0.28, 2.86) 0.58 (0.22, 1.54)

DeBusk et al.	12 m	12/293	10/292	1.20 (0.52, 2.72)	10/293	20/292	0.50 (0.24, 1.05)
Fitzgerald et al.	12 m	35/333	35/335	1.01 (0.65, 1.57)	NR	NR	NR
Cupples et al.	24 m	13/342	29/346	0.45 (0.24, 0.86)	NR	NR	NR
	60 m	47/342	65/346	0.73 (0.52, 1.03)	NR	NR	NR
M-HART	12 m	38/692	27/684	1.39 (0.86, 2.25)	44/692	42/684	1.04 (0.69, 1.56)
Carlsson et al (1998)	12 m	2/118	2/117	0.99 (0.14, 6.92)	NR	NR	NR
Campbell et al.	12 m	22/673	25/670	0.88 (0.50, 1.54)	13/540	12/518	1.04 (0.48, 2.26)
	56 m	100/673	128/670	0.78 (0.61, 0.99)	100/673	125/670	0.80 (0.63, 1.01)
Jolly et al.	12 m	15/277	23/320	0.75 (0.40, 1.42)	NR	NR	NR
Allison et al. (2000)	6m	2/158	2/168	1.06 (0.15, 7.46)	0/158	1/168	0.35 (0.01, 8.63)
COACH pilot	6 m	0/121	2/124	0.20 (0.01, 4.22)	NR	NR	NR
COACH	6 m	4/398	4/394	0.99 (0.25, 3.93)	NR	NR	NR
	48 m	32/398	32/394		NR	NR	NR
ELMI	12 m	1/151	3/151	0.33 (0.04, 3.17)	NR	NR	NR
Young et al	14 m	8/71	11/75	0.77 (0.33, 1.80)	NR	NR	NR
Sub-Total:	***13 trials***	***153/3772***	***173/3831***	***0.90 (0.73, 1.11)***	***72/1828***	***75/1817***	***0.95 (0.69, 1.30)***
TOTAL	**27 trials****	**433/6888**	**477/6737**	**0.89 (0.79, 1.01)**	**299/4714**	**323/4496**	**0.89 (0.77, 1.04)**

***** Data for all trials except that of Campbell et al., DeBusk et al, and Allison et al. are for the combined endpoint of nonfatal and fatal myocardial infarction. The Campbell et al trial only collected data on nonfatal reinfarction rate and total mortality (they were unable to dissect out causes of mortality). The Allison et al and DeBusk et al trials collected data on nonfatal myocardial infarction.

** Note that for PRECOR, there were 2 intervention arms and 1 control arm

NR= not reported, but e-mail sent to PI requesting data if study published within past 10 years

Table 3: Impact of interventions on other endpoints

Study	Major Cardiovascular Risk Factors			Use of proven efficacious therapies	Patient Quality of Life	Patient functional status or symptom scores
	Cholesterol	Smoking	BP			
Comprehensive Cardiac Rehabilitation						
Sivarajan	0	0	0	0	0	0
Vermeulen et al.	++	–	0	0	0	+
Bengtsson	0	0	++	0	–	0
WHO*	++	–	++	++	0	–
Oldridge	0	0	0	0	+	–
PRECOR - comprehensive rehabilitation arm	0	–	0	0	0	++
Fridlund	0	–	0	0	++	++
Engblom	–	++	–	–	++	0
Heidelberg Trial -12 m f/u -72 m f/u	 ++ –	 – –	 0 0	 – –	 0 0	 0 0
Johnston	0	0	0	0	++	++
Lisspers et al.	0	++	0	0	0	0
Sundin et al.	+	0	0	0	0	0
Yu	0	0	0	0	+	+
Vestfold Heartcare Study	–	++	–	–	++	++
Marchionni et al	0	0	0	0	0	++
Group Cardiac Rehabilitation without exercise component						
Stern	0	0	0	0	++	0
PRECOR -counselling arm	0	–	0	0	0	++
Jones et al.	0	–	0	–	–	–
DIET	+	0	0	0	0	0
Individual Counselling						
SCRIP	++	++	+	++	0	0

DeBusk et al.	++	++	0	++	0	++
Fitzgerald et al	0	0	0	0	0	0
Naylor et al. (94)	0	0	0	0	–	–
Cupples et al.	+	+	+	++	0	++
M-HART	0	0	0	0	+	0
Carlsson et al (1997)	0	+	0	0	0	0
Carlsson et al (1998)	++	0	0	++	0	0
Campbell et al. -12m f/u -56 m year f/u	 ++ +	 – –	 ++ +	 ++ –	 ++ –	 ++ –
Jolly et al.	+	–	+	–	–	–
Naylor et al. (99)	0	0	0	0	+	+
Allison et al. (99)	+	++	0	++	0	0
Allison et al. (2000)	+	–	–	–	0	0
Moher et al	++	++	++	–	–	0
Stagmo	+	0	0	+	0	0
McHugh	++	++	++	0	++	++
Higgins et al.	+	–	0	0	0	++
Allen et al.	++	0	0	+	0	0
COACH pilot	++	0	0	–	0	0
COACH	++	–	++	++	++	++
ELMI	–	–	–	0	–	–
Young et al	0	0	0	0	0	0
REACH	–	0	0	–	0	0

Use of proven efficacious therapies" encompasses both increased prescription rate by clinicians and/or increased compliance by patients.

++ Statistically significant benefit seen in the intervention arm vs. control arm.

+ Trend towards better outcomes in the intervention arm, but didn't reach statistical significance.

– No appreciable difference between the intervention arm and control arm.

0 Not reported in study.

Comment [l1]:

Figure 1. Flow of trials through the selection process

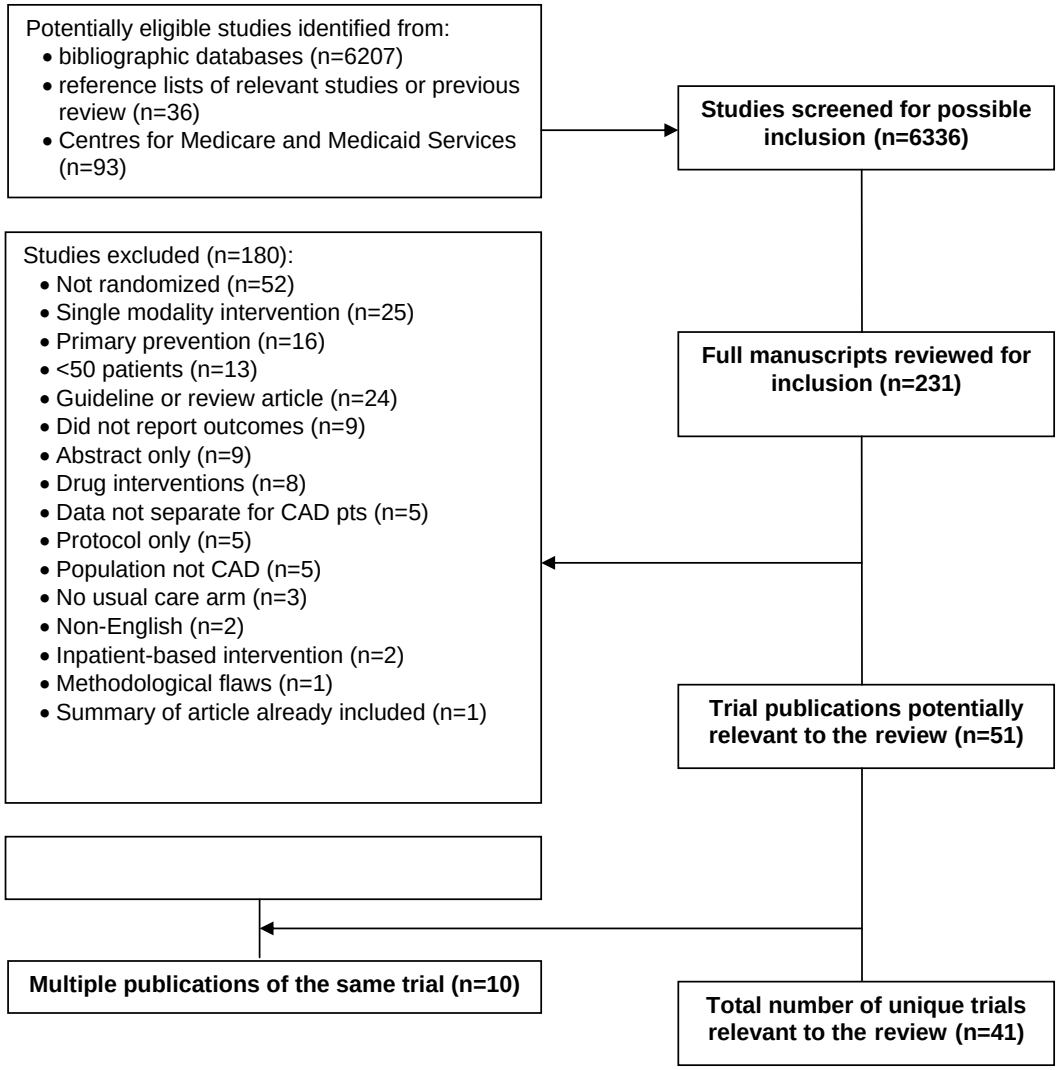


Figure 2: All-cause mortality in trials evaluating comprehensive cardiac rehabilitation

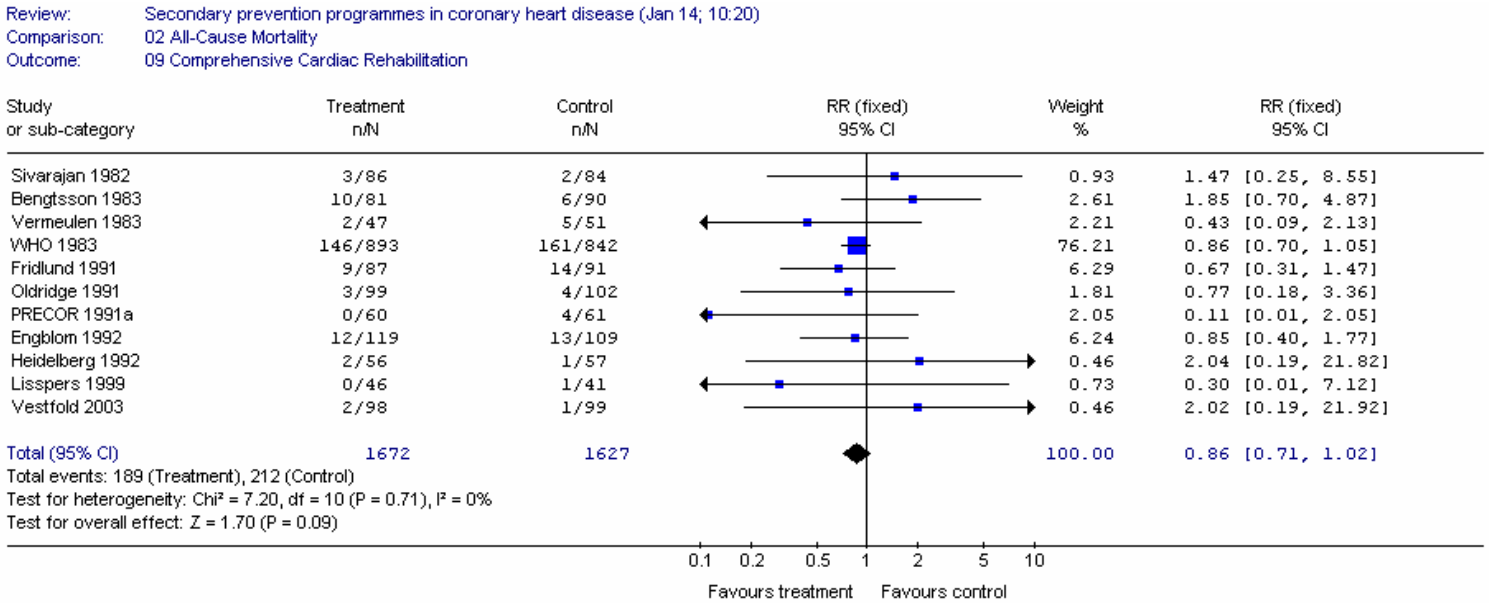


Figure 3: All-cause mortality in trials evaluating group cardiac rehabilitation without exercise component

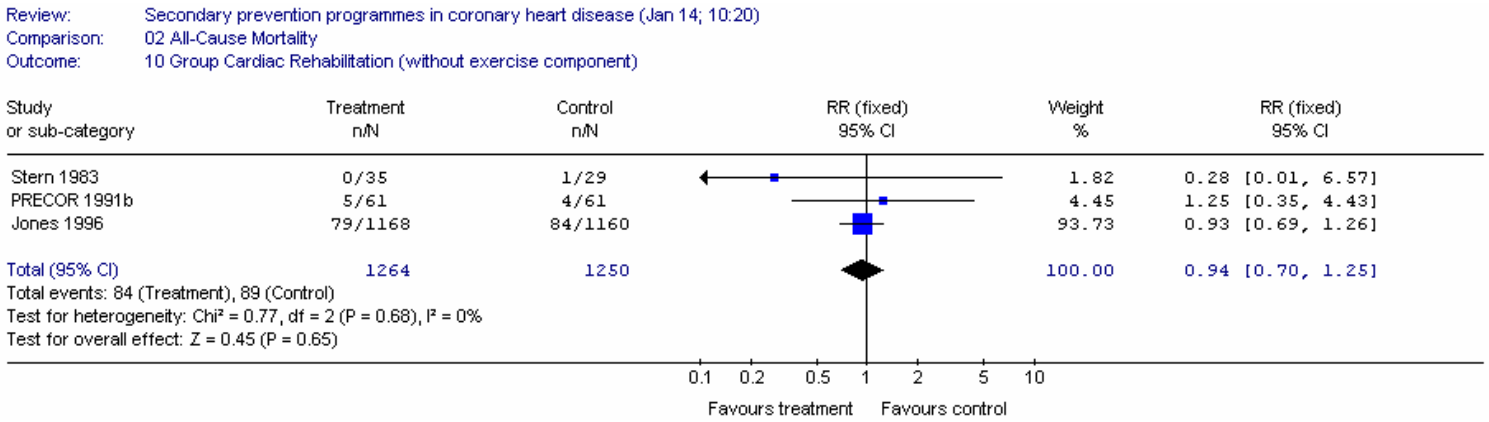


Figure 4: All-cause mortality in trials evaluating individual counselling

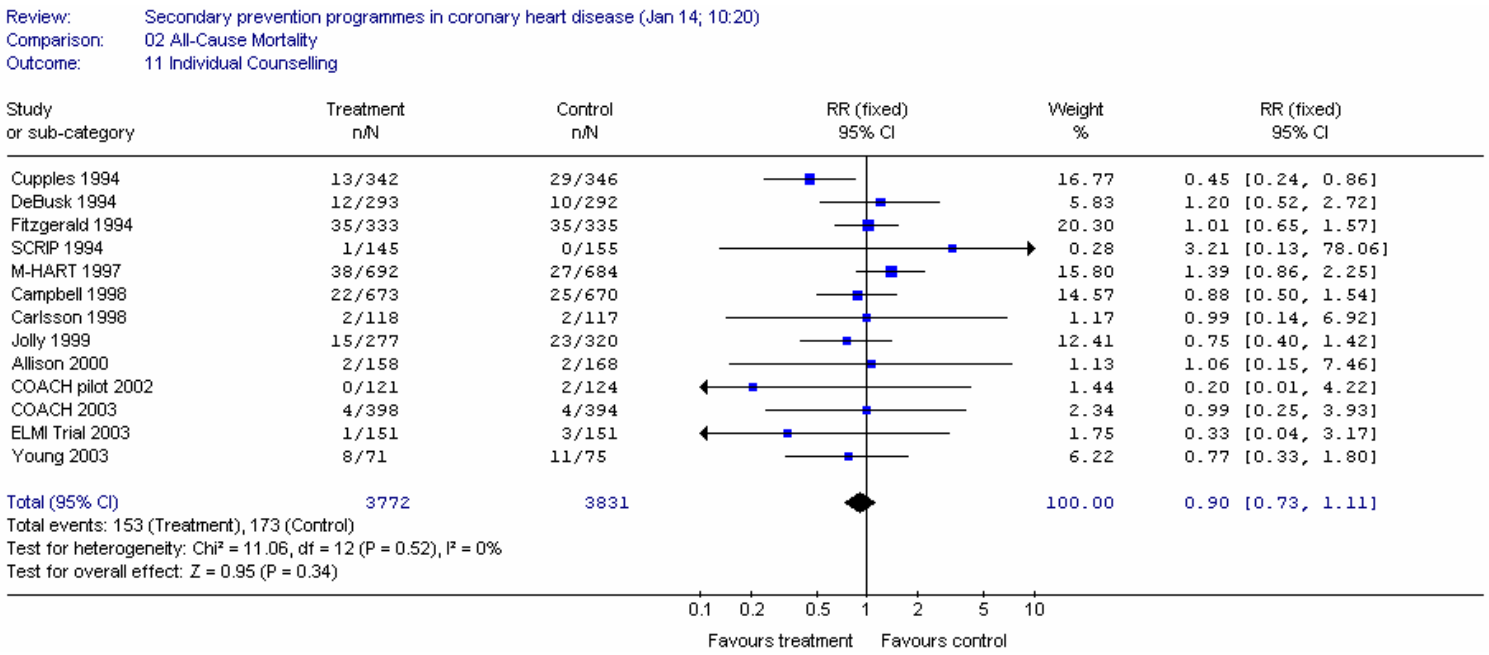


Figure 5: Recurrent myocardial infarctions in trials evaluating comprehensive cardiac rehabilitation

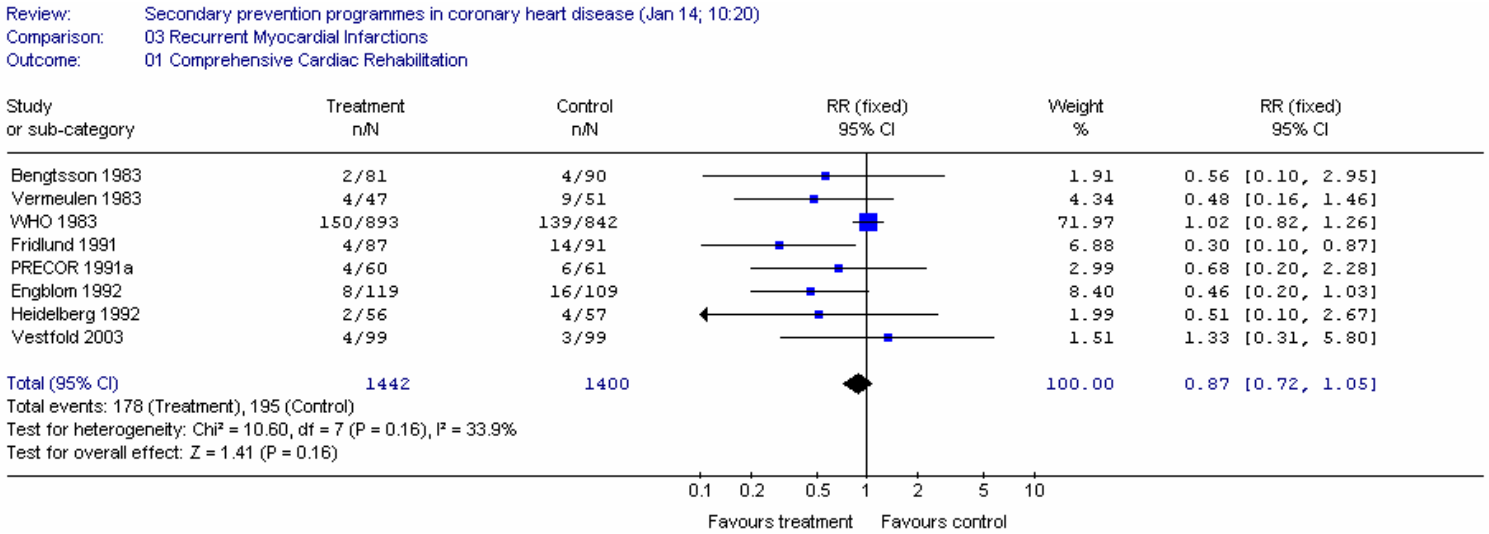


Figure 6: Recurrent myocardial infarctions in trials evaluating group cardiac rehabilitation without exercise component

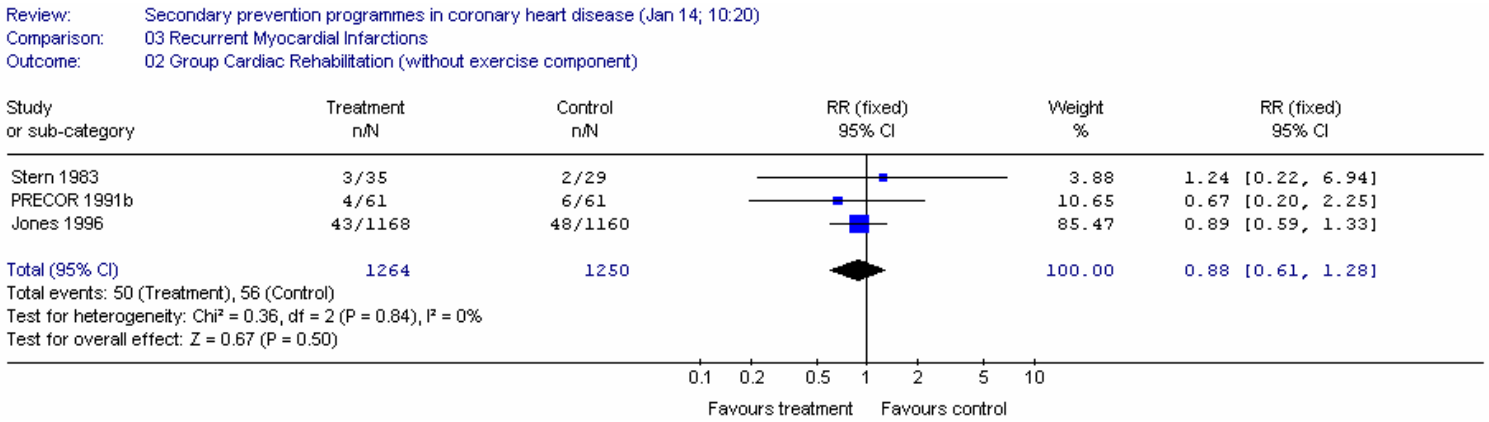


Figure 7: Recurrent myocardial infarctions in trials evaluating individual counseling

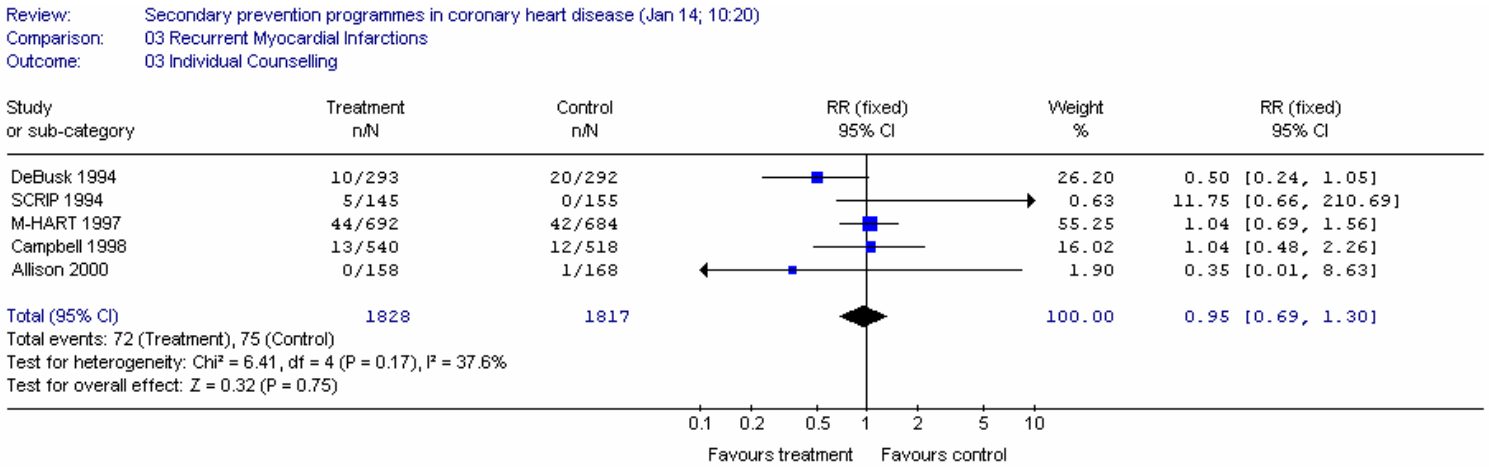
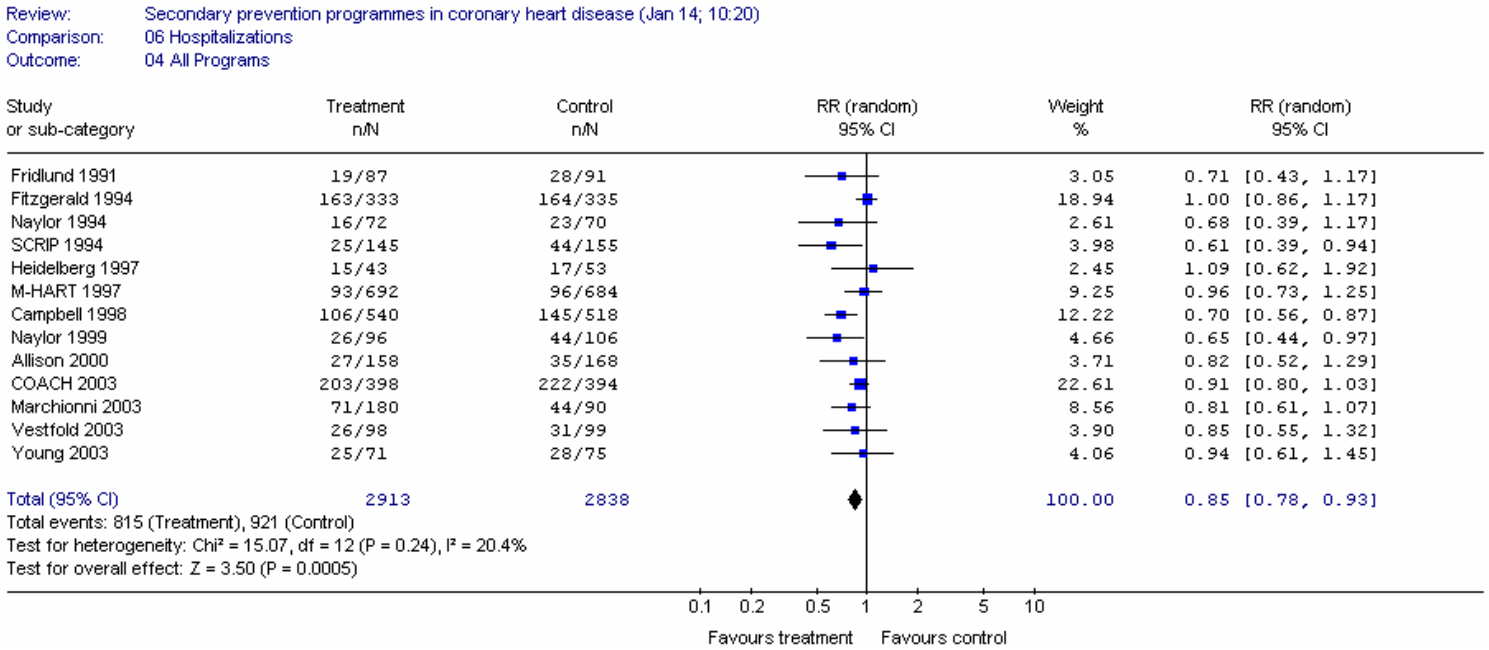
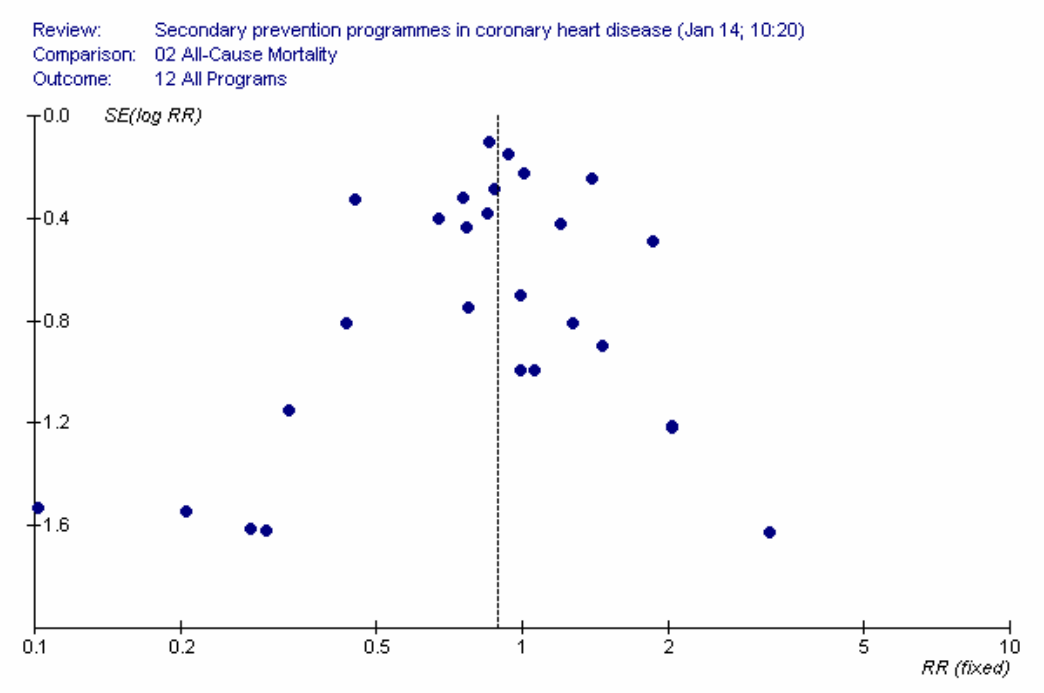


Figure 8: Hospitalization rates in trials evaluating secondary prevention programs



These data depict risk ratios for the number of patients requiring at least one hospitalization during follow-up. RR<1 are consistent with less hospitalizations in the intervention arm; RR>1 are associated with less hospitalizations in the control arm.
Note that the data from some studies (SCRIP, Heidelberg, M-HART, Allison, and COACH) are "cardiovascular hospitalizations" while for the other studies it is "all-cause hospitalizations". E-mails have been sent to authors of studies reporting only "cardiovascular hospitalizations" requesting data on "all-cause hospitalizations". See text for results for "all-cause hospitalization" studies and for "cardiovascular hospitalizations" studies separately.

Figure 9: Funnel Plot for all-cause mortality data



Appendix A. Search Strategies

MEDLINE - Ovid Version: rel9.1.0
Searched December 16, 2004
Results: 2527 unique records

1. exp "Case Management"/
2. exp "Comprehensive Health Care"/
3. exp "Disease Management"/
4. exp "Health Services Research"/
5. exp "Home Care Services"/
6. exp "Clinical Protocols"/
7. exp "Patient Care Planning"/
8. exp "Quality of Health Care"/
9. exp REHABILITATION/
10. (nurse adj led adj1 clinic$).ti,ab.
11. (special$ adj1 clinic$).ti,ab.
12. or/1-11
13. exp "Myocardial Ischemia"/ or "Myocardial Ischemia$".ti,ab.
14. RANDOMIZED CONTROLLED TRIAL.pt.
15. ANIMAL/ not HUMAN/
16. 14 not 15
17. 12 and 13 and 16
18. limit 17 to (english language and yr=1999 - 2005)
19. remove duplicates from 18

- The same search was conducted in **EBM Reviews - Cochrane Central Register of Controlled Trials - Ovid Version: rel9.1.0** (4th Quarter 2004) on December 16, 2004.
- There were 141 unique results.

PubMed
Searched December 16, 2004
Results: 50 unique records

The following search was conducted:

("Case Management"[MeSH] OR "Comprehensive Health Care"[MeSH] OR "Disease Management"[MeSH] OR "Health Services Research"[MeSH] OR "Home Care Services"[MeSH] OR "Clinical Protocols"[MeSH] OR "Clinical Protocols"[MeSH] OR "Patient Care Planning"[MeSH] OR "Quality of Health Care"[MeSH] OR "Rehabilitation"[MeSH]) AND ("Myocardial Ischemia"[MeSH] OR Myocardial Ischemia Field: Title/Abstract)

Limits: Publication Date from 2004/01/01 to 2004/12/17, Randomized Controlled Trial

Web of Science
Searched December 17, 2004
Results: 606 unique records

The **Cited Reference Search** feature was used to search for studies that cited the included studies from the original article.

EMBASE - Ovid Version: rel9.1.0
1988 to 2004 Week 51
Searched December 20, 2004
Results: 1313 unique records

1. exp "Patient Care"/
2. exp "Health Care"/
3. exp "Disease Management"/
4. exp "Health Services Research"/
5. exp "Home Care"/
6. exp "Clinical Protocol"/
7. exp "Health Care Quality"/
8. exp REHABILITATION/
9. (nurse adj led adj1 clinic$).ti,ab.
10. (special$ adj1 clinic$).ti,ab.
11. or/1-10
12. exp "Heart Muscle Ischemia"/ or exp "Ischemic Heart Disease"/ or exp "Coronary Heart Disease"/ or "Myocardial Ischemia$".ti,ab.
13. RANDOMIZED CONTROLLED TRIAL/
14. 11 and 12 and 13
15. limit 14 to english
16. limit 15 to human
17. remove duplicates from 16
18. limit 17 to yr=1999 - 2005

CINAHL (Cumulative Index to Nursing & Allied Health Literature) - Ovid Version: rel9.1.0
1982 to December Week 2 2004
Searched December 21, 2004
Results: 9 unique records

1. exp "Case Management"/
2. *Health Care Delivery/
3. exp "Disease Management"/
4. exp "Health Services Research"/
5. exp Home Health Care/
6. exp Protocols/
7. exp "Quality of Health Care"/
8. exp REHABILITATION/
9. (nurse adj led adj1 clinic$).ti,ab.
10. (special$ adj1 clinic$).ti,ab.
11. or/1-10
12. exp "Myocardial Ischemia"/ or "Myocardial Ischemia$".ti,ab.
13. clinical trial.pt.
14. animals/
15. 13 not 14
16. and/11-12,15
17. limit 16 to yr=1999-2005

SIGLE - FIZ Karlsruhe – Version Interhost 3000
Searched December 21, 2004
Results: 53

CORONARY OR MYOCARDIAL

AND

Health services, health administration, community care services

Appendix B: List of Excluded Studies and Reasons for Exclusion (full references at end of table)

Author year	Source	Reason for exclusion
Ades and Coello 2000	Database (WOS)	Guideline / review article
Akosah, Schaper, Havlik et al 2002	Database	Not randomized
Aldana, Whitmer, Greenlaw et al 2003	CMS	Not randomized
Ammerman, Keyserling, Atwood et al 2003	Database (Medline)	Primary prevention
Angerer, Siebert, Kothny et al 2000	CMS	Not randomized
Anonymous 1982	Database	Primary prevention
Ariyo, Haan, Tangen et al 2000	CMS	Not randomized
Arthur, Daniels, McKelvie 2000	Database (Medline)	Did not report primary outcomes
Barnard, Massey, Cherny et al 1983	CMS	Evaluated interventions which were not comprehensive disease management systems
Barnes, Trieber, Turner et al 1999	CMS	Population not CHD
Bartels, Gerdes, Babin-Ebell et al 2002	CMS	Guideline / review article
Beckie 1989	Database	Did not report primary outcomes
Bennett, Blackall, Clapham et al 1989	Database	Not randomized
Bentsson 1983	Database	Methodological flaw (patients excluded after randomization)
Berglund, Nilsson, Ericksson et al 2000	Database	Primary prevention
Berkman, Blumenthal, Burg et al 2003	Database (Medline)	Evaluated interventions which were not comprehensive disease management systems
Bethell and Mullee 1990	Reference list	Evaluated interventions which were not comprehensive disease management systems
Billings, Scherwitz, Sullivan et al	CMS	Guideline / review article
Bjarnason-Wehrens, Benesch, Bischoff et al 2003	Database (WOS)	Non-English
Blair, Bryant, Bocuzzi 1988	Database	Not randomized
Blumenthal, Jiang, Babyak et al 1997	CMS	Not randomized
Bogden, Koontz, Williamson et al 1997	Database	Did not report primary outcomes

Boulay and Prud'homme 2004	Database (WOS)	Not randomized
Bramlet, King, Young et al 1997	Database	Not randomized
Brown, Zhao, Chait et al 2001	CMS	Drug interventions
Burell	CMS	Guideline / review article
Cambien, Richard, Ducimetiere et al 1981	Database	Primary prevention
Campbell, Ritchie, Thain et al 1998	Database (Embase)	Protocol only
Cannon, Braunwald, McCabe et al 2004	CMS	Evaluated interventions which were not comprehensive disease management systems
Caracciolo, Davis, Sopko et al 1995	CMS	Not randomized
Carlson, Johnson, Franklin et al 2000	Database (WOS)	No usual care arm
Carney, Blumenthal, Stein et al 2001	CMS	Not randomized
Castillo-Richmond, Schneider, Alexander et al 2000	CMS	Evaluated interventions which were not comprehensive disease management systems
Chinaglia, Gaschino, Asteggiano et al 2002	Database	Not randomized
Clark, Bakhai, Lacey et al 2004	CMS	Not randomized
Coleman, Grothaus, Sandhu et al 1999	Database	Did not report the outcomes for patients with CHD separately or included <50% patients with CHD
Corti, Fuster, Fayad et al 2002	CMS	Drug interventions
Coull, Taylor, Elton et al 2004	Database (Medline)	Evaluated interventions which were not comprehensive disease management systems
Council on Clinical Cardiology and Council on Nutrition, Physical Activity and Metabolism 2003	CMS	Guideline / review article
Cummings, Hughes, Weaver et al 1990	Database	Did not report the outcomes for patients with CHD separately or included <50% patients with CHD
Cundiff 2002	CMS	Guideline / review article
DeBusk, Haskell, Miller et al 1985	Database	Evaluated interventions which were not comprehensive disease management systems
DeBusk, Miller, Parker et al 2004	Database (WOS)	Population not CHD
De Lorgeril, Salen, Martin et al 1999	CMS	Evaluated interventions which were not comprehensive disease

		management systems
Denollet and Brutsaert 2001	CMS	Not randomized
Detry, Vierendel, Vanbutsele et al 2001	Database (WOS)	Not randomized
DeVries, Palmer, Scheib et al 2002	CMS	Not randomized
DeVries, Day, Scott 2003	CMS	Not randomized
Diehl 1998	CMS	Not randomized
Dugan, Cohen	CMS	Guideline / review article
Dugmore, Tipson, Phillips et al 1999	Database (Medline)	Evaluated interventions which were not comprehensive disease management systems
Eaker, Sullivan, Kelly-Hayes et al 2004	CMS	Not randomized
Eddy 2000	CMS	Guideline / review article
Ellingsen, Hjermann, Abdelnoor et al 2003	Database (Medline)	Primary prevention
Elliott-Eller, Weidner, Pischke 2003	CMS	Abstract
Engblom, Korpilahti, Hamalainen et al 1997	Database	Did not report primary outcomes
Esposito, Giugliano, Nappo et al 2004	CMS	Drug interventions
Esselstyn 1999	CMS	Guideline / review article
Family Heart Study Group 1994	Database	Primary prevention
Fields, Walton, Schneider et al 2002	CMS	Protocol only
Flanagan, Cox, Paine et al 1999	Database	Not randomized
Frasure-Smith and Prince 1985	Database	Not randomized
Frasure-Smith, Lesperance, Gravel et al 2000	CMS	Not randomized
Friedman, Thoreson, Gill et al 1984	Database	Not randomized
Galatius, Gustafsson, Kistorp et al 2003	Database	Not randomized
Geil, Anderson, Gustafson 1995	CMS	Evaluated interventions which were not comprehensive disease management systems
George and Goldberg 2001	CMS	Guideline / review article
Ghoncheh and Smith 2004	CMS	Population not CHD
Gielen, Schuler, Hambrecht 2001	CMS	Guideline / review article
Gleason, Bourdet, Koehn et al 2002	CMS	<50 patients
Gould, Ornish, Scherwitz et al	CMS	<50 patients

1995		
Gould, Ornish, Kirkeeide et al 1992	CMS	Protocol only
Grimm for the MRFIT 1983	Database	Primary prevention
Grundy, Cleeman, Merz et al 2004	CMS	Guideline / review article
Gulati, Pandey, Arnsdorf et al 2003	CMS	Not randomized
Hakim, Curb, Petrovitch et al 1999	CMS	Evaluated interventions which were not comprehensive disease management systems
Hambrecht, Walther, Mobius-Winkler 2004	CMS	Evaluated interventions which were not comprehensive disease management systems
Harris, Record, Gipson et al 1998	Database	Not randomized
Hedback and Perk 1987	Database	Not randomized
Imperial Cancer Research Fund OXCHECK Study Group 1995	Database	Primary prevention
Jain, Uppal, Bhatnagar et al 1993	CMS	Evaluated interventions which were not comprehensive disease management systems
Jukema, Bruschke, van Boven et al 1995	CMS	Drug interventions
Kawachi, Sparrow, Vokonas et al 1994	CMS	Not randomized
Ketola, Makela, Klockars 2001	Database (WOS)	Primary prevention
Koertge, Weidner, Billings et al 2002	CMS	Abstract
Koertge, Weidner, Elliott-Eller et al 2003	CMS	Not randomized
Kornitzer, De Backer, Dramaix et al 1980	Database	Primary prevention
Krachler	Reference list	<50 patients
Kris-Etherton, Harris, Appel et al 2002	CMS	Guideline / review article
Lampert, Joska, Burg et al 2002	CMS	Not randomized
Lear, Ignaszewski, Linden et al 2002	Database (WOS)	Protocol only
Lesperance, Frasure-Smith, Talajic et al 2002	CMS	Not randomized
Lewin, Furze, Robinson et al 2002	Database (Medline)	No usual care arm
Lewis and Resnik 1967	Database	Did not report the outcomes for

		patients with CHD separately or included <50% patients with CHD
Liao, Ma, Dong et al 2003	Database (Embase)	Non-English
Lichtenstein and Van Horn 1998	CMS	Guideline / review article
Lindholm, Ekbom, Dash et al 1995	Database	Primary prevention
Maggioni 2000	Database (Embase)	Guideline / review article
Malach and Imperato 2004	CMS	Not randomized
Marra, Paolillo, Spadaccini et al 1985	Database	Evaluated interventions which were not comprehensive disease management systems
Marshall, Penckofer, Llewellyn 1986	Database	Not randomized
Matthews, Gump, Harris et al 2004	CMS	Not randomized
Meer 1999	Database (SIGLE)	Not randomized
Meland, Laerum, Ulvik 1997	Database	Primary prevention
Merritt, Scherwitz, Brown et al 1990	CMS	<50 patients
Merritt, Ornish, Scherwitz et al 1995a	CMS	Abstract
Merritt, Ornish, Scherwitz et al 1995b	CMS	Abstract
Merritt-Worden, Pettengill, Ornish 2003	CMS	Abstract
Miettinen, Pyorala, Olsson et al 1997	CMS	Drug interventions
Miller, Erlinger, Young et al 2002	CMS	<50 patients
Mittleman, Maclure, Sherwood et al 1995	CMS	Not randomized
National Cholesterol Education Program, National Institutes of Health	CMS	Guidelines / review article
Ness, Hughes, Elwood et al 2002	Database (Medline)	Evaluated interventions which were not comprehensive disease management systems
Nicholson, Sklar, Barnard et al 1999	CMS	Evaluated interventions which were not comprehensive disease management systems
Oldenburg, Martin, Greenwood 1995	Database	Did not report primary outcomes
Ornish, Scherwitz, Doody et al	CMS	<50 patients

1983		
Ornish, Brown, Scherwitz et al 1990	CMS	<50 patients
Ornish 1998	CMS	Not randomized
Ornish, Scherwitz, Billings et al 1998	Database / CMS	<50 patients
Ornish 2002	CMS	Guideline / review article
Ornish and Pettengill 2003	CMS	Abstract
Ornish 2004	CMS	Guideline / review article
Ornish (chapter 8)	CMS	Guideline / review article
Ornish and Hart (chapter 34)	CMS	Guideline / review article
Pater, Ditlef Jacobsen, Rollag et al 2000	Database (Embase)	Protocol only (no data presented)
Peiss, Kurleto, Rubenfire 1995	Database	Not randomized
Pettengill, Pearson, Pifalo et al 2002	CMS	Abstract
Pfisterer, Buser, Osswald et al 2003	CMS	Not randomized
Picard, Schwartz, Ahn et al 1989	Database	Evaluated interventions which were not comprehensive disease management systems
Pischke, Weidner, Billings J et al 2002	CMS	Abstract
Pitt, Waters, Brown et al 1999	CMS	Drug interventions
Pollock, Franklin, Balady et al 2000	CMS	Guideline / review article
Pozen, Stechmiller, Harris et al 1977	Database	Inpatient-based intervention
Prochaska, Johnson, Lee	CMS	Guideline / review article
Pyke, Wood, Kinmonth et al 1997	Database	Primary prevention
Rahe, Ward, Hayes 1979	Database	<50 patients
Rihal, Raco, Gersh et al 2003	CMS	Guideline / review article
Roderick, Ruddock, Hunt et al 1997	Database	Primary prevention
Roman, Gutierrez, Luksic et al 1983	Database	Evaluated interventions which were not comprehensive disease management systems
Rose, Heller, Pedoe et al 1980	Database	Primary prevention
Rubenstein, Kahn, Reinisch et al 1990	Database	Not randomized
Ruo, Rumsfeld, Hlatky et al 2003	CMS	Not randomized
Scandinavian Simvastatin Survival Study 1994	CMS	Drug interventions

Schectman, Wolff, Byrd et al 1996	Database	Did not report the outcomes for patients with CHD separately or included <50% patients with CHD
Schneider, Staggers, Alexander et al 1995	CMS	Evaluated interventions with were not comprehensive disease management systems
Sdringola, Nakagawa, Nakagawa et al 2003	CMS	Not randomized
Shaffer and Wexler 1995	Database	Not randomized
Shintani, Beckham, Brown et al 2001	CMS	Population not CHD
Simpson, Dixon, Bolli 2004	Database (WOS)	Not randomized
Sivarajan, Newton, Almes et al 1983	Database	Did not report primary outcomes
The South East London Screening Study Group 1977	Database	Primary prevention
Specchia, De Servi, Scire et al 1996	Reference list	No usual care arm
Stahle, Mattsson, Ryden et al 1999	Database (Medline)	Evaluated interventions with were not comprehensive disease management systems
Starkey, Michaelis, Lusignan 2000	Database	Not randomized
Stern and Cleary 1982	Database	Evaluated interventions with were not comprehensive disease management systems
Strandberg, Pitkala, Berglind et al 2001	Database (Embase)	Protocol only (no data presented)
Taddei, Galetta, Virdis et al 2000	CMS	Evaluated interventions with were not comprehensive disease management systems
Thoresen, Friedman, Gill et al 1982	Database	Not randomized
Townsend, Piper, Frank et al 1988	Database	Evaluated interventions with were not comprehensive disease management systems
Tu, Pashos, Naylor et al 1997	CMS	Not randomized
Vale, Jelinek, Best et al 2003	Database (Medline)	Summary of trial already included
Van Drenth, Hulscher, Mokkink et al 1997	Database	Not randomized
Vedin, Wilhelmsson, Tibblin et al 1976	Database	Not randomized
Von Birgelen, Hartmann, Mintz et al 2003	CMS	Not randomized

Wallner, Watzinger, Lindschinger et al 1999	Database (Medline)	<50 patients
Wasson, Gaudette, Whaley et al 1992	Database	Evaluated interventions which were not comprehensive disease management systems
Waters, Higginson, Gladstone et al 1994	CMS	Drug interventions
Weber, Barnard, Roy 1983	CMS	Population not CHD
Weidner, Pischke, Eller 2003	CMS	Abstract
Weinberger, Smith, Katz et al 1988	Database	Did not report the outcomes for patients with CHD separately or included <50% patients with CHD
Weingarten, Reidinger, Conner et al 1994	Database	Inpatient-based intervention
Weintraub, Clements, Crisco et al 2003	CMS	Not randomized
Williams, Paton, Siegler et al 2000	CMS	Not randomized
Woollard, Burke, Beilin et al (Journal of Cardiovascular Risk) 2003	Database (Medline)	<50 patients
Woollard, Burke, Beilin (Journal of Human Hypertension) 2003	Database (WOS)	<50 patients
Yu-Poth, Zhao, Etherton et al 1999	CMS	Guideline / review article

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